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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,193	01/06/2006	Johannes Hubertus Wieringa	2003.796US	7506
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ORGANON USA, INC. c/o MERCK 2000 Galloping Hill Road Mail Stop: K-6-1, 1990 Kenilworth, NJ 07033				
EXAMINER JARRELL, NOBLE E				
ART UNIT PAPER NUMBER				
1624				
NOTIFICATION DATE DELIVERY MODE				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@spcorp.com

### Office Action Summary

**Application No.**

10/564,193

**Applicant(s)**

WIERINGA ET AL.

**Examiner**

NOBLE JARRELL

**Art Unit**

1624

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 September 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 10-13 is/are pending in the application.
- 4a) Of the above claim(s) 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsman's Patent Drawing Review (PTO-940)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

#### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 24 September 2010 has been entered.
2. Claims 10-13 are pending in the instant application.
3. Claim 10 is withdrawn and claims 11-13 are being examined on the merits.
4. The 35 U.S.C. 103(a) rejection is maintained because WO 00/62783 is not being used as a prior art reference.

#### *Claim Rejections - 35 USC § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Burg (US 4062848, issued 13 December 1977, cited previously) in view of Pizey (*Synthetic Reagents, Volume 6, 1985*, pages 270-275 and 372-414) and Collins (*Methods for Obtaining Optically Active Compounds, Chirality in Industry, 1992*, cited in IDS).

***Determining the scope and contents of the prior art***

Van der Burg teaches the synthesis of mirtazapine by the reaction of 1-(3-hydroxymethylpyridyl)-2-phenyl-4-methyl-piperazine (3.25 grams) and 6.5 milliliters (mL) of concentrated sulfuric acid (example I, column 10, line 17 to column 11, line 31). The weight ratio of sulfuric acid (the dehydration agent) to the substrate [1-(3-hydroxymethylpyridyl)-2-phenyl-4-methyl-piperazine] is 2. The product is recrystallized in petroleum ether. Van der Burg also teaches that polyphosphoric acid (PPA), phosphorous pentoxide, and sulfuric acid are each dehydrating agents (column 2, lines 1-15). This teaching says that these three dehydration agents are equivalent. Van der Burg also teaches that the total synthesis described in example 1 can be used with optically active form of compounds of formula II (column 6, lines 48-60). This means that racemic resolution can occur at any stage in the synthetic process. Van der Burg does not describe that racemization is lost in the sulfuric acid step.

Pizey teaches several concepts. The first concept is the use of cosolvents is required when the proportion of PPA to substrate is reduced (normally the proportion is 10-30 times the substrate). One such cosolvent listed is sulfolane, an aprotic polar solvent (page 373). The second concept is that PPA contains phosphorous pentoxide (page 374). This second concept teaches that when PPA is used as dehydration agent, phosphorous pentoxide is also active.

Collins teaches recrystallization is a common technique in organic chemistry (pages 20-21, section 1.2.2.1).

***Ascertaining the differences between the prior art and the claims at issue***

In the current set of claims, the dehydration process of claims 11-13 is done with polyphosphoric acid without solvent, PPA in the presence of either *N*-methylpyrrolidinone or dimethylformamide, or phosphorous pentoxide in the presence of either *N*-methylpyrrolidinone or dimethylformamide.

Van der Burg teaches the preparation of mirtazapine with concentrated sulfuric acid as a dehydration agent. Van der Burg does not teach the explicit preparation of the (S)-enantiomer of mirtazapine.

Pizey teaches that dehydration reactions utilizing PPA (and phosphorous pentoxide) where the ratio of dehydration agent to substrate is less than 10 to 1, a cosolvent is required. Pizey does not teach the synthesis of mirtazapine.

***Resolving the level of ordinary skill in the pertinent art***

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of mirtazapine).

***Considering objective evidence present in the application indicating obviousness or nonobviousness***

System a) of claim 11 is rendered obvious by Van der Burg because the reference teaches the dehydration of a precursor to mirtazapine with an equivalent dehydration agent. Van der Burg states that sulfuric acid and PPA are equivalents in terms of dehydrating agents. In addition, the weight ratio of PPA to substrate is 2, which is less than 2.5:1. System b) of claim 11 and system c) of claim 11 and claim 13 are obvious because Pizey teaches that when the ratio of PPA (which contains phosphorous pentoxide) is less than ten to one, a cosolvent is required. The two cosolvents listed in the claims, *N*-methylpyrrolidinone and dimethylformamide, are both considered polar aprotic solvents. The use of these solvents in the dehydration process is considered obvious because it is considered routine experimentation to use different solvents in a reaction (optimization of conditions). Claim 12 is rendered obvious by Van der Burg because it would be obvious to purify a racemic mixture of products in order to determine which enantiomer has greater effectiveness as an antihistaminic compound (see abstract). Recrystallization is considered routine to obtain specific enantiomers of a compound (Collins, page 20, section 1.2.2.1).

***Conclusion***

8. Claims 11-13 do not appear free over the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 8:30 A.M - 5:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1624

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/  
Primary Examiner, Art Unit 1624